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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,056	06/22/2001	Kenneth Kornman	MSA-023.01	6975

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 09/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,056	KORNMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-16,18-23,26,27 and 38-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-16,18-23,26,27 and 38-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112 – First Paragraph

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 3-7, 9-16, 18-23, 26, 27 and 38-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Enablement Issues

The enablement issues in this application do not revolve around whether it is possible to perform a screening assay which will give results. Screening assays are known. The first issue is that there is significant evidence which disputes the association of the particularly claimed markers with particular disease syndromes and there is general art which suggests that single gene associations are typically wrong. Thus, there is a fundamental "how to use" issue since a screening that compares two patient populations at a specific allele which allele has no impact on inflammation or disease will not provide meaningful results. Second, there is a scope of enablement issue since any one of these alleles is not associated with every disease (and inflammation may include virtually every disease) and any one of these alleles cannot be tied to most of the biomarkers claimed. The claims, but using a Markush set of alleles, function to claim combinations of alleles, diseases and biomarkers which are not disclosed as useful together and which are not enabled by the current specification.

The nature of the invention

The claims are drawn to methods of identification of substances which will affect a biological response in a subject with a particular allele or set of alleles based upon the association of a biomarker response in the subject to the substance. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such

as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are extremely broad. The claims are open to any inflammatory disease, and claim 5 explicitly lists diseases as diverse as periodontal disease, Alzheimer's disease, gastric cancer, asthma, acne, osteoporosis and multiple sclerosis. This list includes disease with dramatically different etiologies, symptoms, whose sole relationship is that they result in inflammation. This breadth is particularly striking given the definition in the specification of "inflammation indicator" as

> "Inflammation indicators may be any of these, and may not even be directly involved in inflammatory responses but nonetheless serve as an indicator of an inflammatory response. With respect to cells, inflammation indicators may be essentially any aspect of cell function, for example levels or rate of production of signaling molecules, transcription factors, intermediate metabolites, cytokines, prostanoids, gene transcripts as well as post-translational modifications of proteins. In subjects, inflammation indicators can be, for example, the response to a subcutaneous injection of urate crystals, electrocardiogram (ECG) parameters, pulmonary function, IL-Iβ, IL-6, C-reactive protein, fibrinogen, hormones, urine parameters, tissue parameters, isolated cell parameters (see page 11 of the specification)."

Thus, the scope of inflammation is literally defined as any aspect of cell function. Since every disease involves some aspect of cell function, the claims arguably encompass every disease. There is no question that the claims expressly encompass any infectious disease, which will directly induce an inflammatory response (and sepsis is expressly claimed in claim 5).

The claim scope breadth is further enhanced by the breadth of biomarkers which can be associated with disease. These biomarkers, listed in claim 7, range from body temperature to blood iron levels. The specification futher increases this claim breadth by including markers such as intermediate metabolites, cellular redox states, mRNA levels and proteome analysis (see page 28 of the specification).

The claims therefore encompass a screening method for substances in which the association of virtually any disease using any change in phenotype with the particular allele set.

Finally, the claims are also drawn to a rather large number of alleles, twenty one different alleles being listed in claim 1.

Quantity of Experimentation

The quantity of experimentation in this area is immense since there is complete variability in the response of association of different alleles with different diseases and different biomarkers. In order to validate the association of a single allele with a single biomarker and a single disease, years of studies with hundreds of patients and replicated clinical trials would be required. When the claims encompass twenty one different alleles, virtually every possible disease (and certainly many hundreds of different syndromes), as well as literally any biomarker, this would require more effor than is expended in the entire NIH budget. For example, it would require significant study and experimentation including trials with hundreds of patients to determine that even a single different allele is truly associated with osteoporosis. A similar study would

be necessary to validate the biomarker chosen as being associated with both the allele and osteoporosis. Only then could the screening assay be reliably performed and expected to provide a result that would have any meaning. These initial validation studies represent inventive, unpredictable and difficult undertakings, and efficacy of any of the polymorphisms, as a diagnostic for any particular disease would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) notes with regard to association of mutations studies that larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). So the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association for these alleles. This is a very large amount of experimentation.

The unpredictability of the art and the state of the prior art

The art is literally replete with specific studies which indicate that specific alleles claimed are not associated with particular inflammatory diseases. It is entirely unpredictable which allele is associated with which disease, if any, and it is further entirely unpredictable which biomarker would function as a surrogate for that allele and

permit identification of compounds that will differentially impact individuals with the particularly claimed alleles.

The specification provides evidence of association for only five alleles, with a variety of different diseases. The remaining alleles lack any support in the specification whatsoever. The art directly contradicts the associations found in the specification and the art teaches that many of the associations indicated in the specification between the five discussed alleles and specific diseases are not replicated.

For example, Bajnok et al (Bone (2000) 27(4) :559-562) notes "Our data do not support the hypothesis that this IL-1RN gene VNTR polymorphism has an impact on bone mass in post menopausal women (see abstract)." The VNTR polymorphism is indicated at page 14 of the specification to be associated with osteoporosis, but Bajnok directly rebuts this result.

The specification at page 14 associates the –889 mutation in IL-1A with periodontal disease, Alzheimers, and juvenile chronic arthritis. However, the art disagrees. With regard to periodontal disease, Riggio et al (J. Clin. Periodontol. (2001) 28 :430-436) notes "No association was found between GEOP (generalized early onset periodontitis) and either IL1A –889 or IL1B +3953 in this study of white European Caucasians (see page 432, column 3)." Riggio concludes "The findings of this study and the other European study (Ehmke et al 1999) bring into double the usefulness of these candidate genes as markers of susceptibility to periodontitis (see page 434, column 2)." With regard Alzheimer's disease, Tsai et al (Neuroscience Letters (2003) 343: 93-96) note "In this study, we found a lack of association between the IL-1A C (-

889)T polymorphism and AD risk, even after stratification according to age. Our negative finding is consistent with recent negative reports conducted in Korean (9) and Caucasian populations (5, 10, 11, 13) but contrasts with other positive reports (1, 3, 7, 8, 12, 14). There may be several explanations for this discrepancy. Firstly, previous reports of a positive association between AD and Il-1A C(-889)T polymorphism could be spurious results. Such findings are inherent to statistical analysis and highlight the need for replication using additional sample populations. (see page 94, column 2)." Thus, Tsai challenges the association of –889 with Alzheimers. Finally, with regard to juvenile chronic arthritis, Donn et al (Rheumatology (1999) 38(2):171-175) notes "We haved studied the –889 mutation in a large group of UK oligo-JCA patients and controls. We did not find any association between alleles of this locus and oligo-JCA. (page 174, column 1)."

The specification at page 14 associates the +4845 mutation in Il-1A with periodontal disease and cardiovascular events. However, with regard to periodontal disease, Gonzales et al (Eur. J. Oral Sci. (2003) 111:395-399) analyzed the +4845 mutation and notes "it is concluded that no significant association between IL-1A and IL-1B polymorphisms with aggressive periodontitis in Caucasians in Northern Europe and Hispanics of Central America was found (see page 399, column 1)." Similarly, with regard to one type of cardiovascular event, abodominal aortic aneurysms, Marculescu et al (Thromb. Haemost. (2005) 94:646-650) notes "In conclusion, these six genetic variants in the interlukin-I gene cluster do not seem to play a clinically relevant role in the pathogenesis of AAA, although we cannot rule out the existence of higher gene-

gene or gene-environment interactions (see abstract)." Marculescu analyzed all five of the mutations listed on page 514, including –889, +4845, -511, +3954, and +2018 and found no association with AAA for any of them.

The specification at page 14 associates the –511 mutation in IL-1B with stennosis and with gastric cancer. However, regarding stennosis, Volzke et al (Clinical Science (2004) 106:35-42) notes "Our present findings that the IL-1a –889 C/T and IL 1B –511 C/T gene polymorphisms were not associated with restenosis is in agreement with the results of a recent study (see page 40, column 1). With regard to gastric cancer, Kato et al (J. Gastroenterol (2001) 36:696-699) notes "The IL-1B –511 genetic polymorphism was not associated with gastric cancer in a multipstep carcinogenesis model (see abstract)."

There are similar results for many of the other polymorphisms for which the specification does not even provide any discussion of disease association. For example, Nishibu et al (J. Dermatol. Science (2002) 29:181-184) teaches that the TNF –308 and –238 polymorphisms are not associated with arthritis or psoriasis (see abstract). Louis et al (Eur. Respir. J. (2000) 16:604-608) teaches that the TNF 308 mutation is not associated with Asthma (see abstract). Moller et al (Neuroscience Letters (2004) 359:195-197) recognize that inflammation is associated with Parkinson's but then show that the –889 mutation in IL-1a is not associated (see abstract). Muhlberg et al (European J. Endocrinol. (1998) 138 :686-690) show tha tthe IL receptor antagonist gene is not assocaited with Graves disease (see abstract).

This extensive survey of the prior art therefore demonstrates that it is entirely unpredictable whether any of the claimed alleles are associated with any of the particular diseases or any particular disease whatsoever. This also supports the conclusion that the association with biomarkers is also entirely unpredictable.

The art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of printout)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

Therefore, the art suggests that there is no necessary correlation between polymorphisms and disease, the art teaches that these polymorphisms are not associated with the specific diseases listed. This supports the conclusion that it is entirely unpredictable whether the polymorphisms disclosed in this specification are associated with any disease.

Given the unpredictability of the association, any screening assay based upon an unpredictable and likely inaccurate association will not give meaningful results since the

premise on which the screening is based is not correct. That is, if gastric cancer patients are compared for their response to compounds relative to controls based upon their genotype as having the –511 alllele, where that association of gastric cancer and the –511 allele is simply contradicted by the art, then no meaningful data can result from the analysis. In order for the screening assay to result in meaningful data, the premise on which it relies must be accurate.

Further, it is entirely unpredictable which biomarkers will be reliably associated with which diseases. This is evidenced by Bajnok, who failed to find an association with the central biomarker for osteoporosis, bone mass, and the specific IL polymorphism under examination. In concord was Donn et al, who failed to find changes in interleukin levels in juvenile chronic arthritis patients (see page 174, column 2), but noted that there was unpredictability between different populations on this measure. It is significantly more unpredictable whether the polymorphism, which Donn did not find to be associated with the disease, would be associated with the levels of interleukin or other biomarkers.

In conclusion, the art teaches the significant unpredictability of polymorphism association with disease not only generally, but with specific polymorphisms claimed. This unpredictability in polymorphisms and in biomarkers supports the determination that there is a significant "how to use" enablement issue since a screening that compares two patient populations at a specific allele which allele has no impact on inflammation or disease will not provide meaningful results.

Working Examples

The specification has no working examples of screening assay. The specification does not specifically demonstrate the association of any biomarkers with any of the specific polymorphisms claimed. The specification relies on the art to show the association of diseases with polymorphisms, but as discussed above, the art is replete with evidence that the particular polymorphisms are not associated with the claimed diseases.

Guidance in the Specification.

The specification provides no guidance on how to resolve the contradictions in the prior art regarding the lack of association of the alleles and any specific inflammatory disease. The specification fails to provide any significant guidance on which biomarkers are associated with which alleles. The specification provides literally no guidance on a complete combination of disease, allele and biomarker. That is, there is not a single disclosure in the specification of a particular disease which is associated with both a particular allele and a particular biomarker.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the association of any particular allele with any particular disease and the association of the allele with any particular biomarker, where there is no teaching in the specification or art of any association for the allele, in concert with the negative teachings regarding the particular polymorphisms by abundant prior art supports a finding of undue experimentation. The specification provides one with no written description or guidance that leads one to a reliable method of associating the claimed alleles with specific diseases and biomarkers and particularly fails to resolve the unpredictability recognized by the prior art in such associations. Further the specification does not provide guidance to overcome art recognized problems in the association of mutations with diseases as shown by Lucentini and Wacholder, among many others. Finally, the quantity of experimentation is immense. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples and the negative teachings in the prior art balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written and that there is no enabled use for the method as claimed.

Response to Arguments

3. Applicant's arguments filed September 14, 2006 have been fully considered but they are not persuasive.

Applicant argues the cited Wand's factors. Applicant first argues that a claim drawn to only inflammatory disease genotypes recited in the claims. However, the specification clearly defines these terms in the broadest possible manner, as discussed in the rejection. Claim 1 does not limit the disease in any particular way whatsoever. The breadth remains immense for these claims. With regard to quantity of experimentation, Wachholder simply demonstrates that the quantity of experimentation is immense. For any particular narrow disease and a particular genotype, the quantity would involve multiple clinical trials. Here, where virtually every disease falls within the scope of claim 1, the number of clinical trials necessary to enable the claim for each of the diseases listed is prohibitively expensive and would require the efforts of thousands of people.

Applicant then argues the unpredictability rejection. Applicant ignores the specific references, which specifically demonstrate that the claimed alleles are not associated with the diseases asserted by the specification, and chooses to address the general references which demonstrate that the state of the art is such that allele associations are unpredictable. The multiple specific references show more than general unpredictability, they show that the actual alleles claimed by Applicant are not associated with the diseases asserted by Applicant. This is the essence of unpredictability.

Applicant argues that generic statements constitute working examples. There are no working examples.

The conclusion of the enablement rejection is maintained and Applicant's arguments are not found persuasive for the reasons given in the rejection and as argued above.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
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9/26/06